Remarks

Claims 31 and 48 are pending in the subject application. By this Amendment, Applicants have indicated that claim 48 is withdrawn from consideration. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 31 and 48 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

As an initial matter, the Office Action indicates that claim 48 is distinct from claim 31 and that there would be an undue search burden if the claims were examined together. Applicants respectfully traverse. Applicants respectfully assert that claims 31 and 48 are different not due to the cited phrase "determining in unrelated individuals whether the association of a plurality of biallelic markers". Applicants note that such a difference is directed not to "core" of the method (*i.e.*, the localization of a gene in candidate genomic region by the means of biallelic markers) but simply to which population the method can be applied. The choice of unrelated individuals does not represent, as indicated by the Office Action, "completely distinct critical features" specific to claim 48 and it does not lead to an undue search burden for examining claim 48. Accordingly, reconsideration and withdrawal of what appears to be a holding of an election by original presentation by the Patent Examiner and the entry and examination of claim 48 is respectfully requested.

Claim 31 is rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Macaubas *et al.* (June 1997). The Office Action indicates that the Macaubas *et al.* discloses a method of sequence analysis demonstrating that DQ1-associated DQCAR alleles have a single C→A nucleotide substitution interrupting the CA repeat array. Applicants respectfully assert that the Macaubas *et al.* reference does not anticipate the claimed invention.

Applicants respectfully submit that Macaubas *et al.* cannot anticipate the claimed invention as it fails to determine "whether the association of a plurality of biallelic markers located in said candidate genomic region with said detectable trait is significantly different than the association of a plurality of biallelic markers located in a plurality of random genomic regions". As the Examiner is aware, in order to anticipate, a single reference must disclose within the four corners of the document each and every element and limitation contained in the rejected claim. *Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991).

It is respectfully submitted that the cited prior art cannot anticipate the claimed invention as it fails to identify a plurality of biallelic markers in both the candidate genomic region and the plurality of random genomic regions that are utilized in determining the statistical significance in the differences of the association of the biallelic markers in these different genomic regions. For example, the Office Action indicates that the reference is directed to the analysis of DQCAR alleles having a **single** nucleotide substitution (Office Action at page 3, paragraph 9; emphasis added) whereas the claim recites determining the association of a plurality of biallelic markers in a candidate genomic region. Thus, it is respectfully submitted that the cited prior art fails to anticipate the claimed invention as it fails to teach or to determine "whether the association of a plurality of biallelic markers located in said candidate genomic region with said detectable trait is significantly different than the association of a plurality of biallelic markers located in a plurality of random genomic regions" since the reference only teaches the identification of a single biallelic marker in a candidate genomic region. Furthermore, the reference fails to teach the identification of any biallelic markers in random genomic regions.

Furthermore, it is submitted that the newly cited prior art fails to anticipate the claimed invention as it compares the variants of a microsatellite region already known to be associated with an HLA gene (1st sentence of the abstract). Further, paragraph 11 of the Office Action provides an incorrect interpretation of Figure 1 and Table 1 since the study allowed the identification of relevant variants by comparing not random genomic regions in different chromosomes (paragraph 11, first sentence of the Office Action), but the same genomic regions in chromosomes isolated from different (unrelated) individuals. Indeed, the cited reference never refers to any "randomness" of the approach but to the analysis of specific, contiguous loci (*DQA1*, *DQB1*, and *DQCAR*; paragraph between pages 635 and 636) that were analyzed in more than 2000 specific chromosomes that were isolated from different populations (*e.g.*, unrelated individuals; see 1st paragraph of right column at page 636 and "HLA Typing" paragraph at page 639) with a two specific of primers ("Microsatellite Amplification and Sequence" paragraph at page 639, primers CAR1 and CAR2).

Moreover, the paragraph cited in the Office Action allegedly demonstrating the relevance of markers in diseases (paragraph 11, second sentence) does not disclose any association between different biallelic markers localizing a gene. Rather, the paragraph provides examples of certain

trinucleotide repeats associated with diseases (*SCA1*, *SCA2*, *FMR1*; see page 638, column 2, lines 2-6). No polymorphisms were actually measured simultaneously and compared in different DNA repetitive sequences for identifying a gene.

Further, Applicants respectfully submit that there is no teaching that the association of the biallelic marker of DQB1*201 is significantly different than the association of various trinucleotide repeats with other diseases nor is there teaching related to association of a plurality of biallelic markers with these various diseases.

Thus, it is respectfully submitted that the reference fails to anticipate the claimed invention as there is no teaching related to the association of a plurality of biallelic markers located in a candidate genomic region with a plurality of biallelic markers located in a plurality of random genomic regions and because the Macaubas *et al.* reference does not consider any random genomic sequence, let alone biallelic markers located inside them. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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